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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/669,833	09/26/2000	Linda S. Mansfield	MSU 4.1-528	2531

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EXAMINER	
BASKAR, PADMAVATHI	
ART UNIT	PAPER NUMBER
1645	

SHORTENED STATUTORY PERIOD OF RESPONSE	MAIL DATE	DELIVERY MODE
3 MONTHS	02/08/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

If NO period for reply is specified above, the maximum statutory period will apply and will expire 6 MONTHS from the mailing date of this communication.

Office Action Summary	Application No.	Applicant(s)	
	09/669,833	MANSFIELD ET AL.	
	Examiner	Art Unit	
	Padmavathi v. Baskar	1645	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *28 February 2005*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) 29 is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) 29 is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. Upon further review and reconsideration of the application, the finality of the action mailed on 2/7/05 is withdrawn.

Amendment

2. Applicant's amendment filed on 2/28/05 is acknowledged and entered.

Status of claims

3. Claim 29 has been amended.

Claims 1-28 and 30-50 have been cancelled.

Claim 29 is pending and currently under examination.

Claim Rejections 35 USC 112, second paragraph

4. The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter, which the applicant regards as his invention.

5. Claim 29 is rejected under 35 USC 112, second paragraph as being vague and indefinite for the following reasons:

Claim 29, is indefinite because it is confusing as step (e) recites the phrase "providing the isolated antibodies to the 16kD and 30 kD antigen together " however, steps (a)-(d are drawn only to the production of "an" antibody, that is a single antibody and the production of antibody to either 16kD or 30 kD antigen, the preamble recites a method of producing an antibody "selected from the group consisting of" and there is no antecedent basis in the claim for producing the two antibodies required in step (e).

Claim Rejections - 35 USC § 112, first paragraph

6. The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

7. Claim 29 is rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. Applicant is referred to the revised guidelines on written description available at <http://www.uspto.gov> (O.G. published January 30, 2001). This is a written description rejection.

Claim 29 is drawn to a method for producing "an" antibody for use as a passive immunity vaccine in horses against "a" (that is a single antibody against a single antigen) *Sarcocystis neurona* antigen selected from the group consisting of 16 (+/-4) kD antigen and 30kD (+/-4) kD antigen, as determined by SDS polyacrylamide gel electrophoresis, comprising: (a) providing a *Sarcocystis neurona* antigen selected from the group consisting of the 16 (+/-4) kD antigen and the 30 (+/-4) kD antigen; (b) admixing the antigen with an adjuvant to produce an admixture (c) immunizing a mammal with a admixture to produce antibodies against antigen;(d) removing serum from the immunized mammal and isolating from the serum the antibody and (e) providing the isolated antibodies to the 16kD and 30 kD antigen together as the passive immunity vaccine in horses.

The specification teaches that "The present invention relates to a vaccine that provides passive immunity *Sarcocystis neurona* comprising polyclonal or monoclonal antibodies against at least one epitope of a 16 kDa (+/-4) antigen and/or 30 (+/-4) kDa antigen of *S. neurona* (page 5, lines 1-11). The specification also teaches that *S. neurona* merozoites were harvested and the antigens were purified by methods known to the art for purifying antigens, i.e., the 16 (+/-4) kDa antigen and/or 30 (+/-4) kDa antigen. These antigens were purified from merozoites by two- dimensional polyacrylamide gel electrophoresis and purified antigens are used to make

monoclonal antibodies or polyclonal antibodies according to conventionally known methods (para bridging pages 33-34).

Although drawn to DNA arts, the findings in University of California v. Eli Lilly and Co., 119 F.3d 1559, 43 USPQ2d 1398 (Fed. Cir. 1997) and Enzo Biochem, Inc. V. Gen-Probe Inc. are relevant to the instant claims. The Federal Circuit addressed the application of the written description requirement to DNA-related inventions in University of California v. Eli Lilly and Co., 119 F.3d 1559, 43 USPQ2d 1398 (Fed. Cir. 1997). The court stated that "[a] written description of an invention involving a chemical genus, like a description of a chemical species, 'requires a precise definition, such as by structure, formula, [or] chemical name,' of the claimed subject matter sufficient to distinguish it from other materials." Id. At 1567, 43 USPQ2d at 1405. The court also stated that a generic statement such as "vertebrate insulin cDNA" or "mammalian insulin cDNA" without more, is not an adequate written description of the genus because it does not distinguish the genus from others, except by function. It does not specifically define any of the genes that fall within its definition. It does not define any structural features commonly possessed by members of the genus that distinguish them from others. One skilled in the art therefore cannot, as one can do with a fully described genus, visualize or recognize the identity of the members of the genus. A definition by function, as we have previously indicated, does not suffice to define the genus because it is only an indication of what the gene does, rather than what it is Id. At 1568, 43 USPQ2d at 1406. The court concluded that "naming a type of material generally known to exist, in the absence of knowledge as to what that material consists of, is not a description of that material." Id.

Finally, the court addressed the manner by which a genus of cDNAs might be described. "A description of a genus of cDNAs may be achieved by means of a recitation of a representative number of cDNAs, defined by nucleotide sequence, falling within the scope of the genus or of a recitation of structural features common to the members of the genus, which features constitute a substantial portion of the genus." Id.

The Federal Circuit has recently clarified that a DNA molecule can be adequately described without disclosing its complete structure. See Enzo Biochem, Inc. V. Gen-Probe Inc., 296 F.3d 1316, 63 USPQ2d 1609 (Fed. Cir. 2002). The Enzo court adopted the standard that "the written description requirement can be met by 'show[ing] that an invention is complete by disclosure of sufficiently detailed, relevant identifying characteristics ....i.e., complete or partial

structure, other physical and/or chemical properties, functional characteristics when coupled with a known or disclosed correlation between function and structure, or some combination of such characteristics. " Id. At 1324, 63 USPQ2d at 1613 (emphasis omitted, bracketed material in original).

The inventions at issue in Lilly and Enzo were DNA constructs per se, the holdings of those cases are also applicable to claim such as those at issue here because a disclosure that does not adequately describe the product, critical to the claimed method, that is the antigen used to produce the antibodies of the passive immunity vaccine, itself logically cannot adequately describe a method of using that product.

Thus, the instant specification may provide an adequate written description of the 16 (+/-4) kd or 30kd (+/-4) kd *Sarcocystis neurona* antigen that is useful for producing antibodies that will provide immunity to horses against *Sarcocystis neurona* per Lilly by structurally describing a representative number of 16 (+/-4) kD antigen and 30kD (+/-4) kD antigen from which antibodies that provide immunity are produced. Alternatively, per Enzo, the specification can show that the claimed invention is complete "by disclosure of sufficiently detailed, relevant identifying characteristics, functional characteristics when coupled with a known or disclosed correlation between function and structure, or some combination of such characteristics."

In this case, the specification does not describe range of 16 (+/-4) kD and 30kD (+/-4) kD *Sarcocystis neurona* antigen that is useful for producing antibodies that will provide immunity to horses against *Sarcocystis neurona* in a manner that satisfies either the Lilly or Enzo standards. The specification does not provide the complete structure of any antigen, nor does the specification provide any partial structure of such antigens, nor any physical or chemical characteristics of the antigens nor any functional characteristics coupled with a known or disclosed correlation between structure and function. Although the specification teaches methods known to the art for purifying antigens from merozoites by two- dimensional polyacrylamide gel electrophoresis and then using the purified antigens to make monoclonal antibodies , it does not describe range of 16 (+/-4) kD and 30kD (+/-4) kD *Sarcocystis neurona* antigen that is useful for producing antibodies that will provide immunity to horses against *Sarcocystis neurona* that would satisfy the standard set out in Enzo because no specific antigen structure is described.

The specification also fails to describe the antigens required for the production of antibodies for passive immunity by the test set out in Lilly. The specification fails to describe any specific antigen within the claimed range of 12 - 20 kD or 26-34 kD that is useful for producing antibodies that will provide passive immunity vaccine to horses against *Sarcocystis neurona*, therefore, it necessarily fails to describe a "representative number" of such species. in addition, the specification also does not describe "structural features common to the members of the genus, which features constitute a substantial portion of the genus."

Thus, the specification does not provide an adequate written description of range of 16 (+/-4) kD or 30kD (+/-4) kD *Sarcocystis neurona* antigen that is useful for producing antibodies that will provide immunity to horses against *Sarcocystis neurona* that is required to practice the claimed invention. Since the specification fails to adequately describe the product critical to the production of the antibodies of the passive vaccine, it also fails to adequately describe the claimed method of producing an antibody for use as a passive vaccine.

Claim 29 does not comply with 35 USC 112, first paragraph because it is not supported by an adequate written description in the specification.

8. Claim 29 is also rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention since there is total lack of written description support for the claimed invention.

Claim 29 is drawn to a method for producing "an" antibody for use as a passive immunity vaccine in horses against "a" (that is a single antibody against a single antigen) *Sarcocystis neurona* antigen selected from the group consisting of 16 (+/-4) kD antigen and 30kD (+/-4) kD antigen, as determined by SDS polyacrylamide gel electrophoresis, comprising: (a) providing a *Sarcocystis neurona* antigen selected from the group consisting of the 16 (+/-4) kD antigen and the 30 (+/-4) kD antigen; (b) admixing the antigen with an adjuvant to produce an admixture (c) immunizing a mammal with a admixture to produce antibodies against antigen;(d) removing serum from the immunized mammal and isolating from the serum the antibody and (e) providing the isolated antibodies to the 16kD and 30 kD antigen together as the passive immunity vaccine in horses..

The specification teaches that "The present invention relates to a vaccine that provides passive immunity Sarcocystis neurona comprising polyclonal or monoclonal antibodies against at least one epitope of a 16 kDa antigen and/or 30 (+4) kDa antigen of *Sarcocystis*

neurona (p. 5, lines 1-11).

The specification also teaches that *Sarcocystis neurona* merozoites were harvested and the 16 (+/-4) kDa antigen and/or 30 (+/-4) kDa antigen were purified by methods known to the art for purifying antigens, i.e., the 16 (+/-4) kDa antigen and/or 30 (+/-4) kDa antigen. These antigens were purified from merozoites by two- dimensional polyacrylamide gel electrophoresis. then the purified antigens are used to make monoclonal antibodies or polyclonal antibodies according to conventionally known methods (para bridging pages 33-34).

One cannot extrapolate the teachings of the specification to the enablement of the claims because the molecular weight of a protein does not uniquely identify a protein and is only an estimate of the protein molecular weight and is subject to numerous variables that cannot be readily be predicted. Therefore, the claim is drawn to a whole multitude of antigens within 12-20 kD and 26-34 KD and it cannot be predicted from the information in the specification which of the whole multitude of antigens will be useful to produce an antibody that will be a passive immunity vaccine against *S. neurona*.

In particular, Kultima et al. (*BMC Bioinformatics* 2006, **7**:475, www.biomedcentral.com/1471-2105/7/475) teach that in two-dimensional gel electrophoresis proteins first undergo isoelectric focusing (IEF) based on their net charge, then an orthogonal second dimension is applied to further separate proteins based on their molecular weight, in the presence of denaturing conditions. Furthermore, Kultima et al teach that two-dimensional gel electrophoresis mainly produces data which enables the investigator to determine whether a particular protein shows an increase or decrease when comparing two different conditions e.g. a diseased state compared to a non-diseased state. However, Kultima et al. teaches that the limited dynamic range and poor reproducibility between gels has been of major concern with traditional two-dimensional gel electrophoresis experiments, see 1st para. of Background Section. Furthermore Bondy et al. (Journal of Chromatography A, 2005, 1080:2-14) teach that although two-dimensional gel electrophoresis, the use of isoelectric focusing and sodium dodecyl sulfate-polyacrylamide gel electrophoresis, is a valuable tool for separating complex protein mixtures, its utility is often limited by lack of quantitative reproducibility, see p. 2, left column. Additionally, Bondy et al. teach that replicate runs of the same sample can have a standard deviation in spot position of the same order of magnitude as the distance between protein spots from complex mixtures, see p. 2, left column. Additionally, Sambrook et al.

(Molecular Cloning, 2nd edition, Cold Spring Harbor Press, 1989, p. 18.47) teach that the determination of molecular weight by SDS-polyacrylamide gel electrophoresis (the second dimension in two-dimensional gel electrophoresis) is only an estimate and modifications of the polypeptide backbone, such as by glycosylation, can have a significant impact on the apparent molecular weight, see p. 18.47, 1st para.

Given the known art known insensitivity, lack of selectivity and known variability of the protein separation results in the method used to describe the proteins of claim 29, one of ordinary skill in the art would not predictably be able to identify the antigen(s) within the claimed multitude of antigens within 12-20 kD and 26-34 kD that will produce an antibody that will be a passive immunity vaccine against *S. neurona*. The specification provides insufficient guidance with regard to these issues and no evidence has been provided which would allow one of skill in the art to make the invention as claimed with a reasonable expectation of success. For the above reasons, it appears that undue experimentation would be required to make and use the claimed invention without clear identification of the proteins that will produce an antibody that will be a passive immunity vaccine against *S. neurona.*

Claim Rejections - 35 USC 103

9. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negative by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(f) or (g) prior art under 35 U.S.C. 103(a).

10. Claim 29 is rejected under 35 U.S.C. 103(a) as being unpatentable over Liang et al 1998 (Infection and Immunity; 66 (5) 1834-1838 in view of Harlow and Lane 1988 (Antibodies; Cold Spring Harbor).

It is noted that the limitation "for use as a passive immunity vaccine" recited in the claim 29 is viewed as a recitation of intended use and therefore are not given weight in comparing the

claim with the prior art. Claim 29 reads on the production of the product *per se*, which is an antibody against *Sarcocystis neurona* antigen selected from the group consisting of 16 (+/-4) kD antigen and 30kD (+/-4) kD antigen,

Given the recitation in section (e) of providing antibody against *Sarcocystis neurona* antigen 16 (+/-4) kD antigen and 30kD (+/-4) kD antigen together, it is assumed for examination purposes that the claim is drawn to production of an antibody against 16 (+/-4) kD antigen or an antibody against 30kD (+/-4) kD antigen and providing the two antibodies together as the passive immunity vaccine in horses.

Claim 29 is drawn to a method for producing an antibody in horses against a *Sarcocystis neurona* antigen selected from the group consisting of 16 (+/-4) kD antigen and 30kD (+/-4) kD antigen, as determined by SDS polyacrylamide gel electrophoresis, comprising: (a) providing a *Sarcocystis neurona* antigen selected from the group consisting of the 16 (+/-4) kD antigen and the 30 (+/-4) kD antigen; (b) admixing the antigen with an adjuvant to produce an admixture (c) immunizing a mammal with a admixture to produce antibodies against antigen;(d) removing serum from the immunized mammal and isolating from the serum the antibody and (e)providing the isolated antibodies to 16 and 30 kDa antigen together as the passive immunity vaccine in horses.

Liang et al 1998 (see figure 1 and page 1835, right column, first paragraph, figure 3 B), teach a method for identifying the pattern of a panel of antibodies to *S. neurona* immunogenic merozoite surface antigens 11 KD, 16kD, 14 kD and 30kD consistently found in horses with neurologic signs typical of equine protozoal myeloencephalitis (EPM) . The art further teaches that detection of *S. neurona* infection by demonstration of reactivity of serum or CSF samples with Sn11, Sn14, Sn16 antigens has been extensively used as a diagnostic tool and is sensitive (P. 1837, column 1). Liang teaches EPM disease occurs only after the merozoite passes through the vascular endothelium of the blood-brain barrier (see discussion in Liang et al 1998) into the central nervous system and is found in the CSF. Liang also teaches that although many horses are found to test positive for the panel of antibodies, only a subset of those that test positive are actually found to have (see page 1834, 3rd para) EPM because the antibodies indicate not only disease but also exposure to infection. Further Liang et al identifies that antisera to the 30kD are also consistently found in horses with neurologic signs typical of EPM and that although these antibodies are not selective for *S.neurona,* they are selective for other Sarcocystis (see page 1837, left column, first paragraph). Thus, the reference teaches as set forth above, however, the prior art does not teach a method of producing antibodies against these proteins or providing antibodies together.

Harlow and Lane1988, specifically teach how to produce antibodies in a method comprising (a) providing antigen (b) admixing the antigen with an adjuvant to produce an

admixture (c) immunizing a mammal with a admixture to produce antibodies against antigen;(d) removing serum from the immunized mammal and isolating from the serum the antibody for use in diagnosis(especially chapters 5 and 8).

It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to use the known isolated antigens Sn11, Sn 14, Sn 16 and Sn 30 as taught by Liang et al to produce the antibodies against the known antigens in a method taught by Harlow and Lane and put them together to assay CSF for the panel of immunogenic proteins, identified by anti-sera consistently found in horses exposed to or infected with *S. neurona,* in order diagnose EPM and to distinguish EPM caused *by S.neurona* infection from other Sarcocystis infections because both misdiagnosis and time would be saved by assaying CSF for the proteins themselves, demonstrating that the merozoites had invaded the nervous system. Further, one would have been motivated to make the antibodies to all of the consistently found antigens that are immunogenic in horses that present with EPM in order to specifically test the CSF for antigen itself in order to distinguish between diseased (i.e., EPM) horses and those that were only exposed to the infection. Given the conventional nature of the production of the antibodies, one would have a reasonable expectation of success in making the antibodies. Further, it would have been prima facie obvious and one would have been motivated to produce antibodies to all of the proteins, including the 30 kD protein for specifically diagnosing EPM caused by *S.neurona* from EPM caused by other *Sarcocystis* species by using the panel of antibodies of the combined references to *S.neurona* 11 kD, 16 kD, 14 kD and 30 kD antigens because not only are the antigens surface antigens found to be consistently immunogenic in EPM caused by S. neurona, but also because the additional data from the 30 kd antigen provides corroboratory information that the infection is a Sarcocystis infection and the inclusion of antibodies to the 30 kD provides assay of all of the entire panel of proteins consistently found to be immunogenic surface proteins in EPM caused by *S. neurona* infection.

Remarks

11. Claim 29 is rejected.

Conclusion

12. Papers related to this application may be submitted to Group 1600, AU 1645 by facsimile transmission. Papers should be transmitted via the PTO Fax Center, which receives transmissions 24 hours a day and 7 days a week. The transmission of such papers by facsimile

must conform to the notice published in the Official Gazette, 1096 OG 30, November 15, 1989. The Right Fax number is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PMR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PMR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PMR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Any inquiry concerning this communication or earlier communications from the Examiner should be directed to Padma Baskar Ph.D., whose telephone number is ((571) 272-0853. A message may be left on the Examiner's voice mail system. The Examiner can normally be reached on Monday to Friday from 6.30 a.m. to 4.00 p.m. except First Friday of each bi-week.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jeffrey Siew can be reached on (571) 272-0787.

SUSAN UNGAR, PH.D
PRIMARY EXAMINER

Padma Baskar Ph.D